I. Obviousness-Type Double Patenting Rejections

Claims 1-4, 6-8 38, and 39 have been rejected under the judicially created doctrine of obviousness-type double patenting as unpatentable over claims 1-3 of copending and commonly owned U.S. Patent No. 08/486,858. To facilitate prosecution Applicants, without acquiescing to this rejection, respectfully request that the double patenting issue be held in abeyance to the time allowable claims are indicated in either case. If, at that time a double patenting rejection exists, Applicants are willing to file a terminal disclaimer.

II(a). § 103 Rejections-*Prima Facie* Case

The Examiner has maintained the rejections of claims 1-4, 6-8, 20, 21 and 35-39 under 35 U.S.C. § 103 as being unpatentable over Temin *et al.* in Gene Transfer, Kucherlapati Ed., Plenum Press, N.Y. pp 149-187 (1986) and Cone *et al. Proc. Natl. Acad. Sci. USA* 81:6349-6353 in view of Bender *et al.* (1987) *J. of Virol.* 61(5):1639-1646. Applicants respectfully request the reconsideration of these rejections in light of the above amendments and the following remarks.

As to the rejection of claims 1-4, 6-8, 20, and 21, Applicants have amended independent claims 1, 10 and 21. As amended these claims are directed to vectors devoid of a selectable marker which (a) comprise a consensus splice acceptor site, and (b) are useful to nonselectively transfect target cells. The other rejected claims are dependent directly or indirectly from the amended claims and therefore incorporate these limitations as well. Neither Temin *et al.* nor Bender *et al.* teach or suggest vectors devoid of a selectable marker which (a) comprise a consensus splice acceptor site, and (b) are useful to nonselectively transfect target cells. Cone *et al.* also does not teach or suggest vectors devoid of a selectable marker which (a) comprise a consensus splice

acceptor site, and (b) are useful to nonselectively transfect target cells. As discussed hereinafter, Cone *et al.* in fact contains a mere inoperative speculation which does not teach or suggest vectors comprising a consensus splice sequence and devoid of a selectable marker which are useful for the transduction of target cells nonselectively.

In the Rule 115 Amendment filed on November 20, 1995, Applicants have argued that the statement in Cone *et al.* relied upon by the Examiner in each and every § 103 rejection is factually unrelated to the vectors and the data provided in that publication and as such the statement is merely an unsupported commentary lacking specific guidance. On that occasion, Applicants also argued that subsequent studies by Cone's coauthor (Dr. Mulligan) revealed that Cone's suggested titer is nearly an order of magnitude lower than the titers actually needed to achieve the practical nonselective introduction of genes into mammalian cells. The Examiner however, afforded little weight to Applicants' argument and elicited supporting evidence in the form of a Rule 132 Declaration.[1]

In the subsequent Rule 116 Amendment filed October 15, 1996, Applicants *inter alia* sought to demonstrate that the retroviral titers of Cone *et al.* were insufficient to effectively transduce mammalian cells without selection. To this end, Applicants introduced a Rule 132 Declaration (dated October 11, 1996) by Dr. Cohen, who is one of the two authors of the Jaffee *et al. Cancer Research* 53:2221-2226 *(1993)* reference made of record, in which 10 mls of retroviral solution (page 2222 col. 1, paragraph 4) were used. The Examiner however, objected to the Jaffee reference insofar that it did not indicate the titer of the retrovirus used and thus was found not dispositive on the issue of whether Cone *et al.* is inoperative thus "*providing no reasonable expectation of success.*"[2] In

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[1]See Office Action dated April 17, 1996.

[2]See Advisory Action dated November 12, 1996, pages 2-4.

the pending Office Action the Examiner has found Dr. Cohen's Declaration insufficient to overcome the rejections because:

> *"[t]he Declaration states that subsequent studies showed that the retroviral titers of Cone were insufficient to effectively transduce mammalian cells without selections and cites the Jaffe reference to support this assertion. No specific statement was found in the Jaffe reference indicating the titer of the retrovirus used. This reference, therefore, provides no evidence regarding the lack of reasonable expectation of success."*

In response to the Examiner's implicit invitation to submit additional evidence as to the titer used in that publication, Applicants respectfully submit the accompanying additional Rule 132 Declaration (the "Cohen Declaration" included herewith as Attachment A), in which Dr. Cohen, one of the authors of the Jaffe *et al.* publication, explicitly states that,

> *"In Jaffee et al. 10 mls of virus at a minimum concentration of $5x10^6$ virus/ml were used. Hence, $5x10^5$ cells were effectively exposed to $5x10^7$ virus."*

Applicants respectfully submit that the Cohen Declaration addresses the Examiner's stated basis for rejection, dispelling any doubt that the difference in titer is a "*true difference in titer*" and not "*simply related to the Jaffe use of 10 mls and the Cone use of 1 ml of virus,*" as pointed by the Examiner at page 11 second full paragraph.

To establish a *prima facie* case of obviousness, three criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the field, to modify the reference or to combine the referenced teachings. Second, there must be a reasonable expectation of success. Finally, the prior art references must teach or suggest all the claims' limitations. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991) has held that the teaching or suggestion to make the claimed combination and the reasonable

expectation of success must be found in the prior art, and cannot stem from applicant's disclosure.

The Examiner has not pointed to a suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the field, to modify the reference or to combine the referenced teachings. The Examiner has supported his rejection with a conclusory statement averring, rather than substantiating, a motivation to combine.

The second requirement in a obviousness *prima facie* case is that there must be a reasonable expectation of success from the combination. (see *Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143, 229 USPQ 182, 187 (Fed. Cir. 1986)). As discussed extensively on the record and based on the newly introduced evidence, Cone *et al.* is inoperative. Thus, one of skill would not have had a reasonable expectation to successfully transduce target cells without a selectable marker.

The third requirement of a *prima facie* case of obviousness is that the prior art references teach or suggest all the claims' limitations. (*In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974)). Independent claims 1, 10 and 21, as amended, are expressly limited to vectors devoid of a selectable marker which (a) comprise a consensus splice acceptor site, and (b) are useful to nonselectively transfect target cells. Claims 2-4, 6-8, and 20 dependent on independent claims 1, 10 and 21 are by definition also limited accordingly.

The present invention teaches the use of a normal or consensus splice acceptor site disclosed in the instant specification at pages 28 and 29. The only splice sites of relevance in the prior art cited are the cryptic (non-consensus) sites utilized by Bender *et al.* which cannot be mapped and are not typical splice sites. Splicing at cryptic splice

sites is not as efficient as splicing at consensus splice sites. See attached pages from Watson *et al.* Molecular Biology of the Gene, Benjamin Cummings Publishing Company, Menlo Park, CA (1988) pages 639-641 (provided herewith as Attachment B). Since Bender *et al.* teaches the use of a selectable marker and utilizes a cryptic (non-consensus) acceptor splice site, Bender *et al.* does not render obvious the claimed invention under controlling law. The significance of the inclusion of a normal or consensus splice acceptor site in the vectors of the invention is further discussed hereinafter.

None of the references relied upon by the Examiner for any of the § 103 rejections on the record, including Bender *et al.* and Cone *et al.*, teach or suggest retroviral vectors which (a) comprise a consensus splice acceptor site, and (b) are useful to nonselectively transfect target cells. Accordingly, none of the references alone or in combination teach or suggest all of the limitations recited in claims 1, 10 and 21 and thus do not render the pending claims obvious. As held in *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) if an independent claim is nonobvious under 35 U.S.C. § 103, then any claim depending therefrom is nonobvious. Hence, dependent claims 2-4, 6-8, and 20 are not obvious either.

Accordingly, because Temin *et al.*, Bender *et al.*, and Cone *et al.* alone or in combination do not teach or suggest the retroviral vectors of claims 1-4, 6-8, 20, and 21, reconsideration and withdrawal of the rejections of these claims under § 103 is respectfully requested.

As to the rejection of claims 38-41 under 35 U.S.C. § 103 as being unpatentable over the same combination of Temin *et al.*, Bender *et al.*, and Cone *et al.*, Applicants traverse the rejection and aver that these claims are patentable for the following as well as the same reasons adduced above.

At page 12 of the pending Office Action, the Examiner has stated that these claims are not patentable because they are directed to "*vectors [which] represent functional homologs or equivalents to those of claim 1*". Applicants are unaware of any reference in the prior art which teaches or suggests a structural relationship between the prior art and the particular elements of the claimed invention. The Examiner is invited to articulate his basis for finding "*the requisite motivation or suggestion to modify* " (see, *In Re Duel* citation reproduced in the Office Action at page 12) the vectors of claim 1 to arrive to those of claims 38-41, as well as the structural elements relied upon in either the prior art or in a Affidavit pursuant 37 C.F.R § 1.104(d)(2).

Applicants aver that Temin *et al.*, Bender *et al.*, and Cone *et al.* alone or in combination do not teach or suggest the specific retroviral vectors of claims 38-41. Accordingly, reconsideration and withdrawal of the rejections of these claims under § 103 are respectfully requested.

Claims 2-4 and 20 are rejected under 35 U.S.C. § 103 as being unpatentable over Temin *et al.* in view of Cone *et al.* as applied to claims 1, 6-8, 20 and 21, and further in view of Bender *et al.*

Neither Temin *et al.* nor Bender *et al.* teach or suggest retroviral vectors which do not contain a selectable marker. Cone *et al.*, as discussed above, does not cure the deficiencies of Temin *et al.* and Bender *et al.*. Accordingly, neither one of these references alone or in combination teach or suggest the retroviral vectors of claims 1, 6-8, 20 and 21. Furthermore, claims 1 and 21 have been amended to be directed to retroviral vectors useful to nonselectively transfect target cells and including a consensus splice acceptor site. For the above reasons and further based on the newly introduced evidence, Applicants aver that the references cited alone or in combination do not teach or suggest retroviral vectors useful to nonselectively transfect target cells

and including a consensus splice acceptor site according to claims 1, 6-8, 20 and 21. Accordingly, reconsideration and withdrawal of the rejections of these claims under § 103 is respectfully requested.

The Examiner has also rejected claims 9 and 20 under 35 U.S.C. § 103 over Temin *et al.* in view of Cone *et al.* as applied to claims 1, 6-8, 20 and 21, and further in view of Kenten *et al.* (WO 86/05807) and Kuo *et al.* (EP Application No. 0 150 735 A2). Applicants respectfully traverse.

Amended claims 1 and 21 are directed to retroviral vectors useful to nonselectively transfect target cells and further including a consensus splice acceptor site. Neither Kenten et al nor Kuo et al teach or suggest retroviral vectors retroviral devoid of a selectable marker, useful to nonselectively transfect target cells, and further including a consensus splice acceptor site. For the reasons stated above Applicants aver that Cone *et al.* fails to cure the inadequacy of either reference. Accordingly, reconsideration and withdrawal of the rejections of these claims under § 103 is respectfully requested.

Claims 10, 11, 17, 18 and 20 are also rejected under 35 U.S.C. § 103 over Temin *et al.* in view of Cone *et al.* as applied to claims 1, 6-8, 20 and 21, and further in view of Emerman *et al.* (1984) *J. Virol.* 50(1):42-49. Applicants respectfully traverse in part and request reconsideration of this rejection for the same reasons stated above.

Claims 10 and 21 as amended are directed to retroviral vectors useful to nonselectively transfect target cells and further including a consensus splice acceptor site. Since Emerman *et al.* does not teach or suggest the construction or use of retroviral vectors useful to nonselectively transfect target cells and further including a consensus splice acceptor site, this rejection is also relying on Cone *et al.* to supply these elements.

Because Cone *et al.* is inoperative as discussed supra, Applicants aver that none of the references alone or in combination teach or suggest the instant invention of amended claims 1 and 10 and of those claims dependant thereon. Applicants respectfully request the withdrawal and reconsideration of these rejections.

The Examiner has also rejected claims 12-15, 20 and 22 under 35 U.S.C. § 103 over Temin *et al.* in view of Cone *et al.* and Emerman *et al.* as applied to claims 11, 11, 17, 18 and 20 and 21, and further in view of Anderson and deVilliers.

Claims 10 and 21 have been amended to be directed to retroviral vectors useful to nonselectively transfect target cells and further including a consensus splice acceptor site. Neither Temin *et al.*, Emerman *et al.*, or Anderson and deVilliers (U.S. Patent No. 4,963,481) teach or suggest the construction, the use of, or the motivation for retroviral vectors that do not encode a selectable marker, useful to nonselectively transfect target cells, and further including a consensus splice acceptor site. Given that Cone *et al.* is inoperative for the reasons stated above, Applicants respectfully traverse and request reconsideration of this rejection for the same reasons stated above.

Claim 22 is rejected under 35 U.S.C. § 103 over Temin *et al.* in view of Cone *et al.* as applied to claims 1, 6-8 and 20 and 21, and further in view of Anderson and deVilliers. Neither Temin *et al.*, nor Anderson and deVilliers alone or in combination teach or suggest the construction, the use of, or the motivation for retroviral vectors that do not encode a selectable marker. Given that Cone *et al.* is inoperative for the reasons stated above, Applicants respectfully traverse and request reconsideration of this rejection for the same reasons stated above. Furthermore, claim 21 has been amended to be directed to retroviral vectors useful to nonselectively transfect target cells and further including a consensus splice acceptor site. None of the references above or in combination teach or suggest the instant invention of amended claim 21 and of those

claims dependent thereon. Applicants respectfully request the withdrawal and reconsideration of these rejections.

In addition, the Examiner has rejected claims 23 and 24 under 35 U.S.C. § 103 over Temin *et al.* in view of Cone *et al.*, Anderson and deVilliers as applied to claim 22, and further in view of Hilberg *et al.* (*Proc. Natl. Acad. Sci. USA* (1987) 84:5232_5236) or Holland *et al.* (*Proc. Nat. Acad. Sci. USA* 84:8662-8666. Neither Temin *et al.*, Anderson and deVilliers, Hilberg *et al.* or Holland *et al.* alone or in combination teach or suggest the construction, the use of, or the motivation for retroviral vectors that do not encode a selectable marker. Applicants aver that Cone *et al.* is inoperative for the reasons stated above. Accordingly, Applicants respectfully traverse and request reconsideration of this rejection for the same reasons stated above. Furthermore, claim 21 has been amended to be directed to retroviral vectors useful to nonselectively transfect target cells and further including a consensus splice acceptor site. None of the references above or in combination teach or suggest the instant invention of amended claim 21 and of those claims dependent thereon. Applicants respectfully request the withdrawal and reconsideration of these rejections.

The Examiner has also rejected claims 25-31, 40 and 41 under 35 U.S.C. § 103 over Temin *et al.* in view of Cone *et al.*, Anderson and deVilliers taken with either Hilberg *et al.* or Holland *et al.* as applied to claims 23 and 24, and further in view of Franz *et al.* or Weiher *et al.* Applicants respectfully traverse. Neither Temin *et al.*, Anderson and deVilliers, Hilberg *et al.*, Holland *et al.*, Franz *et al.* or Weiher *et al.* alone or in combination teach or suggest the construction or use of, or even the motivation for, retroviral vectors lacking a selectable marker. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the rejection on the basis of the inoperativeness of Cone *et al.* discussed above. Furthermore, claim 21 has been amended to be directed to retroviral vectors useful to nonselectively transfect target cells and further including a

consensus splice acceptor site. Hence, none of the references alone or in combination teach or suggest the instant invention of amended claim 21 and of those claims dependent thereon. Applicants respectfully request the withdrawal and reconsideration of these rejections.

II(b). § 103 Rejections-*Surprising Results*

In addition to the arguments set forth in Section II(a) of this response, Applicants aver that the invention of pending claims 1-4, 6-31, and 35-41 provides unexpectedly superior results. Controlling patent law recognized that unexpected results can serve as a basis for patentability of an invention. *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). As argued in the Rule 115 Amendment filed September 18, 1997, the retroviral vectors according to the present invention have a particular configuration which results in **high level expression and concomitant high transduction frequencies** unique to these vectors. In his reply, the Examiner has stated that,

> *"[t]he applicant has not provided any evidence probative of unexpected results. Further, the applicant's claims are not limited to any unexpectedly superior property. Evidence of unexpected results or other secondary considerations may be probative in this case."*[3]

In response to the Examiner's invitation, Applicants wish to call his attention to Krall *et al.* (provided herewith as Attachment C). In that publication, it is empirically shown (in the form of a comparative study) that the MFG vectors of the invention are superior to the other vectors found in the literature because of a **surprisingly increased level of spliced RNA resulting in both long term as well as short term augmented expression of these vectors**. Notably, Krall *et al.* is a comparative study evaluating N2 based

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[3]See pending Office Action dated November 7, 1997, page 16 .

vectors such as that of Bender *et al.* (see page 37, col. 1) *vis a vis* the MFG according to the present invention. In full compliance with the Examiner's invitation (see *supra),* it is noted that independent claims 1, 10, and 21 have been amended to recite the inclusion of the consensus splice acceptor sites which is postulated to be responsible for the increase in splicing efficiency observed (see Discussion pages 43-46).

For these reasons, Applicants aver that the invention of pending claims 1-4, 6-31, and 35-41 provides unexpectedly superior results and respectfully request the reconsideration and withdrawal of the 35 U.S.C. § 103 rejections discussed above.

III. Conclusions

On the basis of the above remarks, this application is believed to be in condition for allowance. Accordingly, reconsideration of this application and its allowance are requested.

A request for a Five (5) Month Extension of Time, up to and including December 1, 1998, is included herewith. Pursuant 37 C.F.R. §1.136(a)(3), the Examiner is authorized to charge any fee under 37 C.F.R. § 1.17 applicable in the instant, as well as in future communications, to Deposit Account No. 08-0219. Such an authorization should be treated as a constructive petition for extension of time in the concurrent as well as future replies.

The Examiner is encouraged to call the undersigned to facilitate prosecution.

Respectfully submitted,
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